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The Journal of Infectious Diseases

PUBLISHED BY THE MEMORIAL INSTITUTE FOR INFECTIOUS DISEASES

VOL. 12

March 1913

No. 2

THE RELATION OF CALCIUM TO ANAPHYLAXIS.*

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In continuing the investigations regarding the etiology of parturient paresis (milk fever), it occurred to the writers that a study of the effect of the intraperitoneal injection of soluble calcium salts on the normal guinea-pig, and whether these salts exert any antianaphylactic action, would be of great interest. So far as we are able to ascertain from an examination of the literature at present available, very little is known concerning the action of intraperitoneal injection of soluble calcium salts upon the lower animals.

When injected directly into the blood, calcium salts seem to be poisonous, their action resembling that of digitalis in some respects. Cushing[†] states that the lime salts penetrate the tissues with difficulty, and are largely excreted through the intestinal epithelium. Soluble calcium salts precipitate proteins, and when perfused through certain tissues, lime salts are retained by a process of selective absorption. It is also known that calcium shows a remarkable antagonism to certain other metals in their action on

* Received for publication January 26, 1913.

† *Pharmacology and Therapeutics*, 1911, p. 571.

the lower animals and on isolated organs and tissues. Thus the action of potassium on the frog's heart is antagonized by calcium, and as pointed out by Meltzer and Auer,¹ calcium shows a remarkably antagonistic effect toward magnesium. Indeed the more thoroughly the whole subject of calcium in its relation to the animal and plant economy has been studied, the more clearly has it been recognized how essential the calcium salts are to the activity of certain phenomena and ferments.

From his studies on anaphylaxis, Besredka² arrived at the conclusion that calcium chlorid is *par excellence* the great anti-anaphylactic. He states that calcium chlorid, when injected the day before the administration of the second dose of serum, prevents the onset of anaphylaxis, when the sensitized guinea-pigs receive the second dose, 0.25 c.c. of serum, by intraperitoneal injection. In this communication he reserved the right to continue his investigation of the arrest of anaphylactic shock, but since this time (1907) we have been unable to find anything further by this author, regarding the use of calcium chlorid as an antianaphylactic. It is of interest to note in this connection that Netter³ has shown that in children the eruption following the injection of serum is greatly reduced by the administration of calcium chlorid on the day of the injection and on the two following days. Rosenau and Anderson⁴ failed to confirm Besredka's observation regarding the protective action of calcium chlorid against anaphylactic shock. According to these last-named observers, no favorable influence upon the anaphylactic state was obtained by the subcutaneous injection of calcium chlorid, the day preceding the second dose of serum. They also found that the toxic principle of horse serum is not altered in any way by calcium chlorid nor did the administration of calcium chlorid to guinea-pigs by mouth, for several days before the second injection, influence the anaphylaxis.

That the five per cent solution of calcium chlorid, used by Rosenau and Anderson, is very irritating when used subcutaneously, and therefore unsuitable for the purpose of demonstrating the

¹ *Am. Jour. of Physiol.*, 1908, 21, p. 400.

² *Compt. rend. Soc. de biol.*, 1907, 62, p. 1053.

³ *Ibid.*, 1906, 60, p. 279.

⁴ U.S. Public Health and Marine Hospital Service *Bull.* 50, 1908.

effect of calcium upon anaphylaxis, is clearly shown by the following experiment.

Four normal adult guinea-pigs received, by subcutaneous injection into the anterior abdominal wall, three cubic centimeters of a five per cent sterile solution of calcium chlorid. Two of these pigs died within 48 hours of acute peritonitis, accompanied by considerable inflammation at the site of the injection. The remaining two pigs developed large abscesses in the anterior abdominal wall. These abscesses ruptured at the end of seven days, leaving rapidly ulcerating sores which opened into the general peritoneal cavity, resulting in the death of the animals, 16 days after the injection of the calcium.

Two¹ of the writers have demonstrated that a 3.25 per cent solution of calcium lactate produced no harmful effects, other than causing abortion, when injected into the peritoneal cavity of the female guinea-pig. It was therefore decided to use this solution in the present investigations. At the beginning of these experiments with calcium lactate, it was observed that while a 3.25 per cent solution of calcium lactate was practically harmless for female guinea-pigs, yet it was very poisonous for male pigs. We have records of eight normal male guinea-pigs which received, intraperitoneally, nine cubic centimeters of the above solution. Of these eight pigs, five died within 24 hours—a mortality of over 62 per cent. On postmortem examination none of the five pigs presented any evidence of injury, nor gross pathological lesions, except a marked congestion of the kidneys. On microscopical examination of the organs of these pigs, one observed in the liver an extensive cloudy swelling of the cells, with greatly distended capillaries of the centrilobular veins; in places these capillaries closely resembled small interstitial hemorrhages; in the kidney there was also cloudy swelling of the epithelium, of the convoluted tubules; in many places the epithelial cells had entirely disappeared; and there were many small and a few large interstitial hemorrhages; in the adrenals, extreme engorgement of the veins and capillaries and minute interstitial hemorrhages.

Smaller doses of the calcium lactate were now used with much better results. Thirteen guinea-pigs, of which eight were males

¹ Kastle and Healy, *Jour. Infect. Dis.*, 1911, 10, p. 378.

and five females, received, intraperitoneally, from 1 c.c. to 4 c.c. of a 3.25 per cent solution of calcium lactate, and suffered no bad after effects.

Experiment 1.—Two normal male guinea-pigs received, intraperitoneally, five cubic centimeters of fresh whole milk. Five weeks later they received, in a similar manner, 10 c.c. of the calcium solution. One of these pigs died within 24 hours following the calcium injection. The other pig stood the calcium injection well, and at the end of 24 hours received, intraperitoneally, four cubic centimeters of fresh skimmed milk. With the exception of a little restlessness, this pig showed no symptoms following the second injection of milk, and remained quiet with no inclination to eat for about five hours, after which it was apparently normal and, remaining so, was returned to the piggery in good health a month later.

Experiment 2.—Ten normal guinea-pigs received, intraperitoneally, five cubic centimeters of fresh horse serum. Twenty-two days later five of these pigs received, intraperitoneally, 10 c.c. of a 3.25 per cent calcium lactate solution. Three of these pigs died within 24 hours following the calcium injection. On the twenty-third day following the initial dose of horse serum, the surviving seven pigs received, intraperitoneally, a second dose of five cubic centimeters of horse serum. Unfortunately the horse serum which was used in this experiment was not very toxic, so that none of the pigs died following the second dose. Those pigs, however, which had received no calcium, showed, with one exception, distinct symptoms of anaphylaxis, such as restlessness, rubbing of the nose and face, followed by prostration within one hour. One pig showed no symptoms whatever, and three hours after the second dose, all were apparently normal. The two pigs which survived the calcium lactate, upon receiving the second dose of horse serum, were restless with rubbing of the nose and face for a few moments only, after which they showed no symptoms whatever, and at the end of three hours were apparently normal.

Experiment 3.—Five young normal male guinea-pigs received, intraperitoneally, a dose which varied from 1 c.c. to 8 c.c. of the above calcium lactate solution. The two pigs receiving 6 c.c. and 8 c.c., respectively, died within 24 hours following the calcium injection. On the following day each of the three surviving pigs received, intraperitoneally, five cubic centimeters of a solution containing equal parts of egg-white and distilled water. At the end of 18 days each of these pigs received, in the usual manner, five cubic centimeters of a solution containing equal parts of egg-white and distilled water. Following this second dose of egg-white, two of these pigs had violent convulsions, while the third had violent respiratory spasms, and all died within 25 minutes. On postmortem examination of these pigs, no evidence of injury nor gross pathological lesions were found.

Experiment 4.—Five somewhat larger male guinea-pigs received, intraperitoneally, five cubic centimeters of the above solution of egg-white. They all stood the injection well. At the end of 18 days, four of these pigs received, in the usual manner, 1 c.c., 2 c.c., 3 c.c., and 4 c.c. of the calcium lactate solution. The fifth pig, used as a control, received no calcium. On the following day all five pigs received, intraperitoneally, five cubic centimeters of the egg-white solution. Three of the four pigs which had received the calcium had distinct symptoms of anaphylaxis, consisting of scratching of the nose, rapid respirations, accompanied in some cases by a clicking sound, and restlessness, but all recovered. The fourth pig injected with

calcium had violent convulsions and died in 21 minutes. The control pig also had violent convulsions and died in 23 minutes. On postmortem examination of these two pigs, no evidence of injury nor gross pathological lesions were found.

Experiment 5.—Six normal female guinea-pigs received, intraperitoneally, five cubic centimeters of a solution containing one part of egg-white and two parts of distilled water. They all stood this injection well. The following day each of two of these pigs received, intraperitoneally, two cubic centimeters of the calcium lactate solution. At the end of six days each of two other pigs received, in the same manner, a similar dose of calcium lactate, and finally, at the end of 15 days, one of the two remaining pigs received a similar dose of calcium. At the end of 16 days all six pigs were in good condition, and all received, intraperitoneally, five cubic centimeters of the above solution of egg-white. Following this second dose the pig which had received no calcium died in convulsions in five and one-half minutes; the two pigs which had received the calcium at the end of 24 hours, following the first dose of egg-white, died in convulsions in 33 and 56 minutes, respectively; one of the two pigs which had received the calcium at the end of six days died in convulsions in 19 minutes, while the other of these two pigs showed some mild symptoms, and recovered; finally, the pig receiving the calcium 24 hours before the second dose of egg-white also presented mild symptoms of anaphylaxis, and also recovered.

Experiment 6.—Three male guinea-pigs, which had survived from the fourth experiment and which had been protected against the second dose of egg-white through the action of calcium, received, intraperitoneally, five cubic centimeters of fresh undiluted cat serum. Fourteen weeks later two of these pigs received, in the usual manner, two cubic centimeters of the calcium solution. They both stood the injection well, and on the following day they all received 2.5 c.c. of fresh cat serum. The pig which had received no calcium had mild convulsions, and died very quietly in three and one-half hours; of the two pigs which had received calcium, one had slight convulsions and died very quietly in two and one-quarter hours; the other had slight symptoms of anaphylaxis, and recovered.

CONCLUSIONS.

As a result of the above experiments the following three conclusions seem inevitable: first, that a five per cent solution of calcium chlorid used subcutaneously is much too irritating to allow of a fair estimate of the value of calcium as an antianaphylactic; second, that an isotonic solution of calcium lactate used intraperitoneally, in large doses of 5-10 c.c., is very poisonous to male guinea-pigs, the mortality being over 62 per cent; third, that an isotonic solution of calcium lactate used intraperitoneally, in small doses of 1-4 c.c., and at the proper time, does protect guinea-pigs from the anaphylactic shock resulting from milk, horse serum, egg-white, and cat serum. In the first experiment, in which milk was used, the fact that only one pig survived the calcium leaves the question somewhat in doubt, although it is

quite reasonable to infer that the calcium saved the second pig. In the second experiment, in which horse serum was used, there is again doubt, due to the fact that the horse serum was not very toxic. In the third, fourth, and fifth experiments, however, there is no room for doubt. In these experiments egg-white was employed as the anaphylactic agent with a mortality of 88.9 per cent, whereas the mortality from the second dose of egg-white, following the injection of an isotonic solution of calcium lactate, was only 20 per cent.

The writers, therefore, are disposed to agree with Besredka that the use of calcium in the proper doses and at the proper time does protect the animal against anaphylactic shock.

These investigations are being continued.